Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
J 10020 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/008057	19.07.2004	17.07.2003
International Patent Classification (IPC) or national classification and IPC		
C07K7/00, C07K7/06		
Applicant		
JERINI AG		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 40 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/008057

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-115 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* 1-61 received by this Authority on 11.11.2005 with letter of 11.11.2005

nos.* _____ received by this Authority on _____

☐ the drawings:

sheets _____ as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 20-23

because:

☐ the said international application, or the said claims Nos. _____
relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 20-23

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/008057

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	19, 43-61	YES
	Claims	1-18, 24-42	NO
Inventive step (IS)	Claims	19, 43-61	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-19, 44-61	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Reference is made to the following documents:

D1: MARCH DARREN R ET AL: "Potent cyclic antagonists of the complement C5a receptor on human polymorphonuclear leukocytes. Relationships between structures and activity" MOLECULAR PHARMACOLOGY, Vol. 65, No. 4, 1 April 2004 (2004-04-01), pages 868-879, XP002315628 ISSN: 0026-895X

D2: WO 2004/035079 A1 (THE UNIVERSITY OF QUEENSLAND, SHIELS, IAN, ALEXANDER; TAYLOR, STEVEN) 29 April 2004 (2004-04-29)

D3: WO 90/09162 A (ABBOTT LAB) 23 August 1990 (1990-08-23)

D4: WO 92/12168 A (ABBOTT LAB) 23 July 1992 (1992-07-23)

D5: WO 99/00400 A (FAIRLIE DAVID; UNIV QUEENSLAND (AU); WONG ALLAN (AU); FINCH ANGELA) 7 January 1999 (1999-01-07)

D6: FINCH ET AL: "Low-Molecular-Weight Peptidic and Cyclic Antagonists of the Receptor for the Complement Factor C5a" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, Vol. 42, No. 11, 3 June 1999 (1999-06-03)

pages 1965-1974, XP002137173 ISSN: 0022-2623

D7: WO 03/033528 A (TAYLOR STEVE; UNIV QUEENSLAND (AU); SHIELS IAN ALEXANDER (AU)) 24 April 2003 (2003-04-24)

D8: WONG A K ET AL: "Small molecular probes for G-protein-coupled C5a receptors: conformationally constrained antagonists derived from the C terminus of the human plasma protein C5a" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, Vol. 41, No. 18, 27 August 1998 (1998-08-27), pages 3417-3425, XP002200381 ISSN: 0022-2623

D9: DEMARTINO JULIE A ET AL: "Arginine 206 of the C5a receptor is critical for ligand recognition and receptor activation by C-terminal hexapeptide analogs" JOURNAL OF BIOLOGICAL CHEMISTRY, Vol. 270, No. 27, 1995, pages 15966-15969, XP002272328 ISSN: 0021-9258

D10: WO 03/085448 A (KIM BONG-JU; TAE SEUNG-GYU (KR); KIM HYUN-YOUNG (KR); YOON JOO-SUN) 16 October 2003 (2003-10-16).

D1: Antagonist derivatives of C5a receptor, having mainly C-terminal arginine, but also a C-terminal replacement by tyrosine (applicant analyses in the present application show that this peptide would have an IC_{50} value of 0.17 uM whereas the corresponding peptide in the present application would have an IC_{50} of 1.3 uM)

D2: Antagonist derivatives of anaphylotoxin (=C5a) receptor ligand, having mainly C-terminal arginine, but also a C-terminal replacement by

phenylbutanoyl (applicant analyses in the present application show that this peptide would have an IC_{50} value of 2.6 uM)

D3: Antagonist derivatives of C5a receptor having C-terminal Arg

D4: Antagonist derivatives of C5a receptor. Arg replaced by I-Arg, hArg, K and Cit or L-canavinine. No D- or L-lysine, D- or L-homolysine, or glycine. Size of the substitutent at this position is important for high receptor affinity. The citrulline compound has no charged side chain, yet still possesses appreciable antagonist potency compared to arginine at this position.

D5: Cyclic peptide-antagonist of C5a receptor, having a C-terminal arginine, cyclized by backbone to backbone cyclization, no increase in receptor affinity and antagonist potency; AcF[OPdChaWR] with IC_{50} = 2OuM against a max. cone, of C5a (100 uM) on intact human PMN.

D6: C5a receptor antagonists being conformationally constrained and derived from the C-terminus of the human plasma protein C5a

D7: Whole C5a receptor: Arg 206 requires receptor activation by hexapeptides and hexapeptide C-terminal arginine is required for receptor activation. However, as there are also des-arg C5a receptors the situation might be different.

1. The amendments to claims 18 and 42, submitted with the new claims, now satisfy PCT Article 19, since they were restricted to an IC_{50} value of less than

200 uM.

2. The present application does not meet the requirements of PCT Article 33(1) because the subject matter of claims 1-18 and 24-42, and of subjects dependent thereon is not novel within the meaning of PCT Article 33(2) since the peptides disclosed in the prior art would appear to be encompassed by, for example, the general formulation "mimics the biological properties of the tryptophan units", etc.

3. The applicant should further note that the search was directed only to those parts of the claims which can be considered clear and concise, that is to say, the peptides of claim 44, the cyclic C5a receptor antagonists in claim 19, the linear C5a receptor antagonists in claim 43 and the content of claims 45-61, which are dependent on the above claims.

The search carried out in respect of the generalizations in the main claims 1-18 and 24-42, which relate to a disproportionally large number of possible linear and cyclic peptides, was incomplete. The general formulas x1-x2-x3-x4-x5-x6-x7-x8, the Y definition (for example claim 35), the possible presence of bonds which are not ionic/covalent (but coordinative), and the substitution of amino acids with -CH_2(aryl/heteroaryl) of unknown size, include virtually all possible substitution and mimicry

possibilities as well as their derivatives and analogues, partly linked to functionally desirable functions (... mimics the biological properties of a tryptophan unit), in such a way that they appear unclear or worded too generally within the meaning of EPC Article 84 to such an extent as to make a meaningful search impossible. No search could be carried out either in respect of the atom distances in the substance claims (20-23).

4. The novelty of claims 19, 43 and 44, and claims 45-61, which are dependent thereon, must likewise be recognized.

5. The present application satisfies the requirements of PCT Article 33(1) because the subject matter of claims 19 and 43-61 involves an inventive step within the meaning of PCT Article 33(3).

For the purpose of the assessment with regard to the inventive step of the subject matter of the application, *which concerns cyclic and linear derivatives of peptide antagonists of the C5a receptor having a C-terminal arginine exchange in (des-Arg), by X6=Trp, Phe, Tyr, His, 1-naphylalanine, benzothienylalanyl, 2-aminoindane-2-carboxylic acid, 2-thienylalanine, 3-thienylalanine, 3-thienylalanine, 2-fluoro-phenylalanine, 4-fluoro-phenylalannine, 2-chlorophenylalanine, 3-chlorophenylalanine, 4-chlorophenylalanine,* it must be assumed that a person skilled in the field of C5a receptors

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

searching for further effective C5a antagonists and taking into consideration document D7 (in particular page 44, lines 28 ff., citrulline), which can be considered the closest prior art, would assume that in the case of the known D-Arg derivatives of the C5a receptor antagonists of the prior art (for example D5) D-Arg can be replaced with I-Arg, hArg, K, Cit or L-Canavinine. The applicant's attention is further drawn to the fact that non D- or L-lysine, D- or L-homolysine or glycine derivatives are possible. Although the size of the substituents in this position and the receptor affinity thereof are likely to play a role, document D7 offers nothing to suggest that a hydrophobic side chain should be found (see definitions for substituent F in claims 19 and 43).

With the above as point of departure, although citrulline has considerable antagonist potency it suggests the use of other amino acids, for example aromatic/heterocyclic amino acid without a charged side chain, such as tryptophan, phenylalanine, histidine, etc.

Furthermore, documents D6, D8 and D9 demonstrate that, owing to the novel type II beta-turn formations disclosed therein, Trp and Phe must likewise be considered key amino acids for the receptor binding, in addition to, for example, p-Cha and D-Arg (document D8, page 3423, left-hand column). In the light of the overlapping

activities (see also the analysis on pages 4-7) with respect to the prior art, the application clearly shows how specific the selected peptide antagonists are.

The chosen combination of the definitions under F and the IC_{50} of less than 200 uM must not be considered an obvious selection.

A generalization going beyond the definition of F must, however, always be considered speculative.

6. In the light of possible further new substances encompassed by claims 1-18 and 24-42, which at present are not considered novel, the applicant's attention is drawn to the fact that these possible new substances do not necessarily benefit from a possible inventive step of the compounds of claims 19 and 43-61 (PCT Article 33(1)) since the generalizations do not necessarily fully apply to the broad, general formulas. There is justified doubt as to whether a representative number of peptides encompassed by these broad claims does indeed have the desired antagonistic C5a receptor activity. Even if a suitable test was available, it would still be unreasonably difficult for a person skilled in the art to determine whether this is the case for the claimed possible number of compounds. Doing so would be alike to carrying out a research program without clear instructions as to which of the vast number of possible structural modifications in the peptide area the

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

desired antagonistic activity should bring about or delimit further.

In the light of the requirements of PCT Article 5 and 6 it should likewise be taken into consideration that the number of possible peptides encompassed by one of the general claims should be reasonable. The situation may never arise in which it is not clear to a person skilled in the art reading the claims which peptides are encompassed by the claims and which are not.